Risk Markers for Thrombocytopenia in Critically Ill Patients: A Prospective Analysis

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Study Objective. To identify independent risk markers for thrombocytopenia in critically ill patients.

Design. Prospective, observational study.

Setting. Eleven-bed intensive care unit–coronary care unit (ICU-CCU) in a community hospital.

Patients. Three hundred sixty-two consecutive patients meeting inclusion criteria during 1 year.

Intervention. Potential risk marker data were collected on admission to the ICU-CCU and for the period before development of thrombocytopenia (defined as two or more consecutive platelet counts < 150 x 10^3/mm^3 obtained at least 12 hours apart), or for the duration of ICU-CCU stay if thrombocytopenia did not develop.

Measurements and Main Results. Thrombocytopenia developed in 68 patients (18.8%). Multivariate logistic regression analyses identified patients at risk on admission, but the predictive potential of the regression model improved when all risk marker exposures during the ICU-CCU stay were considered. Independent risk markers included fresh frozen plasma administration, sepsis, musculoskeletal diagnosis, pulmonary artery catheter insertion, gastrointestinal diagnosis, packed red blood cell administration, and nonsurgical respiratory diagnosis. Higher admission platelet count and aspirin administration were associated with a lower risk of thrombocytopenia. Heparin administration was not identified as a risk marker, and no patient developed heparin-induced thrombocytopenia with thrombosis. Patients with thrombocytopenia had longer ICU-CCU and hospital stays, and higher ICU-CCU and hospital mortality than those without thrombocytopenia.

Conclusions. Development of thrombocytopenia in critically ill patients is associated with specific diagnoses, packed red cell and fresh frozen plasma transfusions, pulmonary artery catheter insertion, and admission platelet count.

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Thrombocytopenia is common in critically ill patients and is associated with increased duration of hospital stay and increased mortality.[1–6] Although a moderate decline in platelet count does not present a serious risk to most patients, clinicians often intervene in an attempt to prevent life-threatening outcomes associated with severe thrombocytopenia or heparin-induced thrombocytopenia (HIT) with thrombosis. A wide range of causes of thrombocytopenia such as drug therapies, diagnoses, and procedures have been reported in the literature[7, 8]; but study results have been inconsistent, making treatment decisions difficult. Drug therapies, especially

heparin, often are discontinued when thrombocytopenia develops, despite evidence indicating that most patients are not at risk for drug-related adverse events.[2, 4, 9, 10]

Several investigators have attempted to identify the most important risk markers for thrombocytopenia in critically ill patients, but analyses generally have been limited by small samples, retrospective design, and a limited scope of variables assessed.[1–5] In addition, the use of various definitions for thrombocytopenia has made it difficult to compare results. A clear understanding of the most important risk markers for thrombocytopenia in critically ill patients would provide a basis for evidence-based treatment decisions in this area. Hence, we assessed the relative contribution of risk markers suspected to be associated with the development of thrombocytopenia in critically ill patients.

Methods

Protocol

This study was carried out at Lions Gate Hospital, a 350-bed community institution. Approval was obtained from the Ethics Committees for Human Experimentation at Lions Gate Hospital and the University of British Columbia. The need for informed consent was waived since this was an observational study that did not influence the care of patients involved. Consecutive patients admitted to the 11-bed intensive care unit–coronary care unit (ICU-CCU) from June 11, 1997–June 11, 1998, were evaluated by using a prospective, observational study design. Thrombocytopenia was defined as two or more consecutive platelet counts less than 150 x 10^3/mm^3 obtained at least 12 hours apart.

All patients older than 18 years were included in the study if they had two or more platelet counts obtained at least 12 hours apart during their ICU-CCU stay. For patients with more than one admission to the ICU-CCU, only the first admission during the study period was considered. Exclusion criteria included a platelet count less than 150 x 10^3/mm^3 on admission to the unit, concomitant participation in another study, and an admitting diagnosis strongly associated with thrombocytopenia including congenital thrombocytopenia, hypersplenism, mechanical heart valve, disseminated intravascular coagulation, idiopathic thrombocytopenic purpura, or thrombotic thrombocytopenic purpura. Patients who developed these diagnoses during their ICU-CCU stay were included in the analysis.

Potential risk marker data were collected on admission to the ICU-CCU and for the period before development of thrombocytopenia, or for the duration of the ICU-CCU stay if thrombocytopenia did not develop. Data were collected for variables previously identified or suspected to be associated with the development of thrombocytopenia, including patient demographics, history of alcohol abuse, diagnoses, laboratory indexes, organ dysfunction, transfusions, and procedures.[1–5, 7] A comprehensive record of administration of any of 73 drugs previously identified as potential risk markers for thrombocytopenia (list available from the authors) was maintained for all study patients.[1, 2, 4, 7, 11, 12] All heparin exposure was accounted for including heparin administered for maintaining patency of intravenous catheters and heparin coating on pulmonary artery catheters. Heparin exposure up to 8 weeks before ICU-CCU admission was determined from patient interviews, previous health records, and the provincial prescription database. If heparin was discontinued in a patient with thrombocytopenia, the prescribing physician was interviewed to determine whether thrombocytopenia was the reason for discontinuation.

Diagnostic categories were based on the most common *International Classification of Diseases, Ninth Revision*[13] codes reported by the hospital's medical records department for the ICU-CCU during the 2-year period immediately before beginning data collection. These categories were

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nervous system disorders, respiratory surgery, nonsurgical respiratory disorders (including acute respiratory distress syndrome), vascular surgery, acute myocardial infarction, unstable angina, other nonsurgical cardiovascular disorders (including heart failure and arrhythmias), gastrointestinal disorders, gastrointestinal bleeding, musculoskeletal disorders (including trauma), endocrine disorders, diabetes mellitus (including diabetic ketoacidosis), genitourinary disorders, infection (temperature > 38.5°C and white blood cell count > 11 x 10^3/mm^3, or if the patient was given antibiotics for infection, excluding sepsis), sepsis (as defined by the American College of Chest Physicians and Society of Critical Care Medicine[14]), malignancy, and drug overdose. Detailed definitions of each diagnosis are available from the authors.

History of alcohol consumption was determined through discussion with the patient, family, and/or the attending physician. Moderate-to-high alcohol consumption—three or more drinks daily—was evaluated as a risk marker in view of previous reports suggesting that this level of alcohol intake may be associated with thrombocytopenia and platelet dysfunction.[7, 15, 16]

Renal dysfunction was defined as an estimated creatinine clearance of less than 30 ml/minute/72 kg or a 50% decrease in creatinine clearance (from first serum creatinine measurement in the ICU-CCU) as calculated by the modified Cockcroft and Gault equation normalized for weight.[17] Patients were considered to have hepatic dysfunction if liver function test results were elevated to a magnitude previously associated with thrombocytopenia[2]: greater than 5 times the hospital's upper normal limit for liver aminotransferase levels or alkaline phosphatase, or greater than 3 times the hospital's upper normal limit of total or direct bilirubin. If these tests were not performed, hepatic function was assumed to be normal.

Clinical outcomes occurring during the index hospital stay were recorded, including the occurrence of hemorrhage (at least a 1-g/dl decrease in hemoglobin level over 24 hrs plus clinical evidence of bleeding), thrombosis (deep vein thrombosis, pulmonary embolism, myocardial infarction, or ischemic stroke), duration of ICU-CCU stay, duration of hospital stay, ICU-CCU mortality, and hospital mortality.

Statistical Analysis

Logistic regression analysis was carried out and reported according to published guidelines.[18, 19] Data were stored and analyzed by using SPSS version 9.0 (SPSS Inc., Chicago, IL). Univariate analyses were carried out to identify candidate variables for the multivariate regression analysis. Dichotomous variables were analyzed with the χ^2 test, whereas continuous variables were analyzed with the Wald statistic for the logistic regression model. Variables with an exposure frequency of less than 5% were excluded from analysis. Since the univariate tests were used to screen variables, rather than to test a specific hypothesis, a p value of 0.25 was used as the threshold for entry into the multivariate model. Tests were performed for colinearity among variables selected for multivariate analysis and for linearity of selected continuous variables. Candidate variables were entered into a backward stepwise multivariate logistic regression model. Variables were selected for removal by using a p value of 0.10 as the significance level. Interactions between variables within the models were explored, and regression diagnostics were done to identify outliers and influential observations based on standard definitions.[18] For any outliers or influential observations identified, data were reviewed to confirm accurate and complete data entry.

Two regression models were developed. The first model identified risk markers associated with the development of thrombocytopenia during ICU-CCU stay attributed to patient variables present on admission to the ICU-CCU (admission model). For the second model, the diagnoses most responsible for ICU-CCU stay were used and all potential risk markers were considered including those present on admission and those encountered during the ICU-CCU stay (comprehensive model). Clinical outcomes were compared between patients with and those without thrombocytopenia by using the independent *t* test for continuous variables and χ^2 analysis for dichotomous variables

Results

During the 12-month study period, 935 patients were admitted to the Lions Gate Hospital ICU-CCU. Of these, 362 met the criteria for inclusion in the study. Five hundred seventy-three patients were excluded for the following reasons: fewer than two platelet counts (432 patients), admission platelet count less the 150 x 10^3/mm^3 (78), repeat admission (24), measurement of only two platelet counts within 12 hours (21), enrollment in another study that randomly

Table 1. Characteristics of the 362 Study Patients

Characteristic	Value
	Mean ± SD
Age (yrs)	63.2 ± 15.4
Weight (kg)	76.2 ± 17.2
APACHE II score	15.4 ± 9.4
Admission platelet count (x 10^3/mm^3)	246 ± 79
	No. (%)
Gender	
Men	229 (63.2)
Women	133 (36.7)
Caucasian	317 (87.6)
History of moderate-to-high alcohol intake	42 (11.6)
Location immediately before ICU-CCU	
Emergency department	242 (66.9)
Ward	101 (27.9)
Other hospital	19 (5.2)
Cardiac diagnosis[a]	190 (52.5)
Acute myocardial infarction	98 (27.1)
Other nonsurgical cardiovascular	56 (15.5)
Unstable angina	36 (9.9)
Intensive care diagnosis[a]	172 (47.5)
Respiratory, nonsurgical	52 (14.4)
Infection	17 (4.7)
Gastrointestinal	15 (4.1)
Nervous system	14 (3.9)
Sepsis	13 (3.6)
Drug overdose	13 (3.6)
Musculoskeletal	12 (3.3)
Respiratory, surgical	11 (3.0)
Gastrointestinal bleed	10 (2.8)
Vascular surgery	7 (1.9)
Diabetes mellitus	4 (1.1)
Malignancy	4 (1.1)

APACHE = acute physiology and chronic health evaluation; ICU = intensive care unit; CCU = cardiac care unit.
[a]Diagnosis most responsible for stay in CCU or ICU, as defined in Methods.

assigned patients to receive heparin or hirudin (11), age younger than 18 years (5), and admission with disseminated intravascular coagulation (2).

The diagnoses most responsible for ICU-CCU stay were distributed evenly between cardiac and intensive care diagnoses. The most common admission diagnoses were myocardial infarction, other nonsurgical cardiovascular disease (e.g., heart failure, rhythm disturbance), and nonsurgical respiratory disease. Mean admission platelet count was well within the normal range, and mean acute physiology and chronic health evaluation (APACHE) II score (15.4 ± 9.4) indicated moderate disease severity (Table 1). In general, APACHE II scores range from 0–55, with scores of 10–20 representing moderate disease severity.[20]

Occurrence of Thrombocytopenia

During the data collection period, 68 patients (18.8%, 95% confidence interval [CI] 14.8–22.8%) developed thrombocytopenia based on the a priori definition. Mean ± SD onset of thrombocytopenia was 2.9 ± 4.0 days after admission to the unit (range 1–34 days, median 2.0 days). Frequency of thrombocytopenia for patients in the CCU was 8.9% (95% CI 4.9–12.9%) and for patients in the ICU, 29.7% (95% CI 22.9–36.5%). By using different thresholds, some of which were used in previously published research on this topic,[1–5] the frequency of thrombocytopenia for the entire cohort was 3.6–26.5% (Table 2). Platelet counts reported by the Lions Gate Hospital laboratory had an inter- and intraday variability of 11% and 3%, respectively.

Risk Markers for Thrombocytopenia in the Admission Model

Thirteen admission variables were selected for multivariate analysis based on univariate test results. These 13 variables were age, moderate-to-high alcohol consumption, APACHE II score,

Table 2. Occurrence of Thrombocytopenia by Various Definitions

	No. (%) of Patients		
Definition	Entire Cohort (N=362)	Cardiac Diagnosis (n=190)	Intensive Care Diagnosis (n=172)
At least one platelet count			
< 150 x 10^3/mm^3	96 (26.5)	33 (17.4)	63 (36.6)
< 100 x 10^3/mm^3	28 (7.7)	1 (0.5)	27 (15.7)
< 50 x 10^3/mm^3	13 (3.6)	1 (0.5)	12 (7.0)
At least two consecutive platelet counts			
< 150 x 10^3/mm^3	68 (18.8)	17 (8.9)	51 (29.7)
< 100 x 10^3/mm^3	23 (6.4)	1 (0.5)	22 (12.8)
< 50 x 10^3/mm^3	12 (3.3)	1 (0.5)	11 (6.4)

Table 3. Risk Markers Independently Associated with Thrombocytopenia in the Admission Model

Variable	Odds Ratio	95% CI	p Value
Sepsis	14.1	2.9–67.9	0.001
Gastrointestinal diagnosis	7.6	2.1–27.9	0.002
Gastrointestinal bleed	6.7	1.6–29.3	0.011
Musculoskeletal diagnosis	5.9	1.6–21.4	0.007
Nonsurgical respiratory diagnosis	2.3	1.0–5.1	0.005
APACHE II score[a]	1.1	1.1–1.1	<0.001
Age[b]	0.9	0.8–1.0	0.01
Admission platelet count[c]	0.5	0.4–0.7	<0.001

CI = confidence interval.
[a]Per 1-unit increment.
[b]Per 5-year increment.
[c]Per 50 x 10^3/mm^3 increment.

admission platelet count, surgery in the previous 24 hours, and admission diagnoses of myocardial infarction, gastrointestinal disease, gastrointestinal bleeding, musculoskeletal disease, nervous system disease, respiratory disease, sepsis, and unstable angina.

Following multivariate modeling, eight independent admission risk markers for the development of thrombocytopenia were identified (Table 3). An odds ratio (OR) greater than 1 indicates that, controlling for the other variables in the model, the odds of developing thrombocytopenia were greater for patients with that characteristic, diagnosis, or exposure. The degree to which the risk is increased is the value of the OR. For example, for patients with a diagnosis of sepsis on admission, the odds of developing thrombocytopenia during their ICU-CCU stay was 14.1 times higher than those who did not have a diagnosis of sepsis on admission. Some ORs are expressed per increment (i.e., APACHE II, age, and admission platelet count in this model). In these cases, for every unit increase in that variable, the odds of developing thrombocytopenia increased by the value of the OR. For example, for each 1 unit increase in APACHE II score, the odds of developing thrombocytopenia increased by 1.1. Odds ratios less that 1 indicate a decreased risk of thrombocytopenia by the same principles just described.

The area under the receiver operating characteristic (ROC) curve (C statistic) was 0.85 (95% CI 0.80–0.90), indicating good association between the predicted probability of developing thrombocytopenia and the actual observed cases of thrombocytopenia (closer to 1.0 indicates better predictive probability). The ROC curve is calculated by using the model sensitivity and specificity at various cut points to provide an indication of how well the model discriminates between those who did and those who did not develop thrombocytopenia.[21] The Hosmer-Lemeshow goodness-of-fit-test p value equaled 0.52, indicating the model was a reasonable fit of the observed data ($p>0.05$ indicates acceptance of the null hypothesis that there is no significant difference between estimated and observed frequencies).[18]

Risk Markers for Thrombocytopenia in the Comprehensive Model

When exposures during the ICU-CCU stay were considered in addition to admission characteristics, univariate analyses yielded 25 candidate variables for regression analysis: admission platelet count; age; APACHE II score; history of moderate-to-high alcohol consumption; hepatic dysfunction; surgery within the previous 24 hours; pulmonary artery catheter insertion; packed red blood cell transfusion; fresh frozen plasma transfusion; mean heparin dose; exposure to aspirin, imipenem, salbutamol, inotropes, cephalo-sporins, or histamine H_2-receptor antagonists; and diagnoses most responsible for ICU-CCU stay of myocardial infarction, gastrointestinal disease, gastrointestinal bleed, infection, musculoskeletal disease (11 of 12 patients had trauma), nervous system disease, nonsurgical respiratory disease, sepsis, and unstable angina.

Multivariate regression analysis identified nine independent risk markers for thrombocytopenia (Table 4). Interpretation of the ORs follows the same principles described in the previous section. The presence of each risk marker substantially increased or decreased the probability of developing thrombocytopenia (Figure 1). The

Table 4. Risk Markers Independently Associated with Thrombocytopenia in the Comprehensive Model

Variable	Odds Ratio	95% CI	p Value
Fresh frozen plasma transfusion	20.0	2.0–199.3	0.01
Sepsis	15.1	3.1–74.4	0.001
Musculoskeletal diagnosis	9.5	2.6–34.6	0.001
Pulmonary artery catheter	8.4	3.9–17.9	<0.001
Gastrointestinal diagnosis	4.1	1.1–16.0	0.04
Packed red blood cell transfusion	2.5	0.9–6.7	0.07
Nonsurgical respiratory diagnosis	2.3	0.9–5.7	0.07
Aspirin	0.4	0.2–1.0	0.04
Admission platelet count[a]	0.4	0.3–0.6	<0.001

CI = confidence interval.
[a]Per 50 x 10^3/mm^3 increment.

presence of several risk markers increased the predicted risk even more dramatically. For example, the regression model predicted that a patient admitted with a platelet count of 200 x 10^3/mm^3 who developed sepsis and had a pulmonary artery catheter placed had a 94% predicted probability of developing thrombocytopenia, based on our definition. No two variables were highly correlated, including packed red blood cell and fresh frozen plasma administration (Pearson correlation coefficient 0.41). Although the quantity of packed red blood cells and fresh frozen plasma transfusions varied among patients with thrombocytopenia (packed red blood cells: median 2 units, range 1–12 units; fresh frozen plasma: median 2 units, range 2–8 units), these were analyzed as dichotomous variables because of the limited number of patients exposed. The Hosmer-Lemeshow goodness-of-fit-test p value equaled 0.15, and the area under the ROC curve (C statistic) improved slightly, compared with that of the admission model, to 0.89 (95% CI 0.85–0.93).

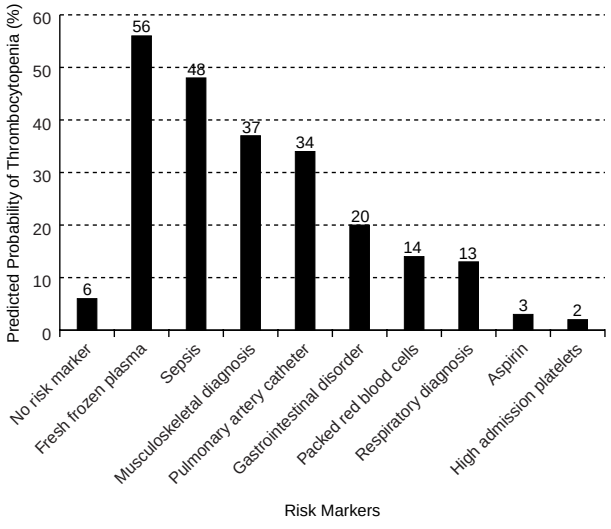

Figure 1. Predicted probability of developing thrombocytopenia for patients with individual risk markers in the comprehensive model. "No risk marker" assumes the platelet count is equal to the sample mean (246 x 10^3/mm^3). For "High admission platelets," the platelet count is 1 SD above the sample mean (i.e., 325 x 10^3/mm^3).

To further test the risk of thrombocytopenia associated with heparin, heparin was entered into the regression model using several dichotomous variables: any exposure, low-dosage exposure (< 1000 U/day), medium-dosage exposure (1000–16,000 U/day), and high-dosage exposure (> 16,000 U/day). Heparin also was analyzed as a continuous variable by using the mean dose/day. In the resultant models, heparin was not a statistically significant independent risk marker, and the predictive ability of the model showed no improvement.

Clinical Outcomes

Twenty-six patients (7.2%) had a hemorrhage at some time during their ICU-CCU stay; however, the frequency of hemorrhage subsequent to thrombocytopenia was lower than the overall frequency in patients without thrombocytopenia. Patients with thrombocytopenia had longer mean lengths of ICU-CCU stay (12.3 ± 13.5 vs 4.5 ± 4.8 days, p<0.001) and hospital stay (32.0 ± 39.0 vs 14.5 ± 18.3 days, p<0.001), as well as a higher ICU-CCU mortality (17.6% vs 4.4%, p<0.001) and hospital mortality (22.1% vs 7.8%, p=0.001) than those without thrombocytopenia (Table 5). Of the 57 patients receiving heparin when thrombocytopenia developed, 10 (18%) had heparin discontinued specifically because of thrombocytopenia (according to the prescribing physician) within 24 hours of the first platelet count below 150 x 10^3/mm^3. Four of these 10

Table 5. Clinical Outcomes in Patients with and Those without Thrombocytopenia

Outcome	Thrombocytopenia (n=68)	No Thrombocytopenia (n=294)	p Value
Hemorrhage, no. (%)	2 (2.9)[a]	11 (3.7)	0.003
Thrombosis, no (%)	3 (4.4)[a]	4 (1.4)	<0.001
Length of ICU-CCU stay, mean ± SD (days)	12.3 ± 13.5	4.5 ± 4.8	<0.001
Length of hospital stay, mean ± SD (days)	32.0 ± 39.0	14.5 ± 18.3	<0.001
ICU-CCU mortality, no. (%)	12 (17.6)	13 (4.4)	<0.001
Hospital mortality, no. (%)	15 (22.1)	23 (7.8)	0.001

[a]After developing thrombocytopenia.

patients were bleeding before or on the day of developing thrombocytopenia.

Three patients with thrombocytopenia developed thrombosis; however, none appeared to have HIT. One patient had not received heparin during his ICU-CCU stay or within the previous 8 weeks. The other two patients had received heparin but had negative results from two assays recommended for the diagnosis of HIT: the ^{14}C-serotonin release assay and the enzyme-linked immunosorbent assay for heparin-dependent antiplatelet antibodies.[22]

The relatively high frequency of hemorrhage before thrombocytopenia (19.1%) in this study and the identification of bleeding episodes as a risk marker for thrombocytopenia in another study[5] prompted further investigation of bleeding as a potential risk marker. Logistic regression analysis was carried out with the candidate variables identified by the original univariate analyses for the comprehensive model, with bleeding episodes (hemorrhage plus gastrointestinal bleeding) replacing gastrointestinal bleeding; however, the predictive performance of the model was not improved.

Discussion

The risk markers identified in this study were derived from the first, to our knowledge, large prospective database specifically designed to collect information relevant to thrombocytopenia in this population. Variables associated with a higher risk of thrombocytopenia in the comprehensive model included specific diagnoses (sepsis, musculoskeletal, gastrointestinal, and respiratory), fresh frozen plasma and packed red blood cell transfusions, and pulmonary artery catheter insertion. No drug, including unfractionated heparin, was identified as a positive independent risk marker.

The frequency of thrombocytopenia in this study was much higher for patients in the ICU than for patients in the CCU, which is consistent with previous studies in these populations.[1–5, 23] The frequency reported in this study is difficult to compare with those in previous reports because of the wide range of definitions used; however, several other studies of critically ill patients have used a definition of one platelet count less than 100 x 10^3/mm^3.[1–5] With this definition, reported frequencies ranged from 13%[3] to 41%,[4] and in our study the frequency was 15.7% in the ICU population (Table 2). The wide range of reported frequencies likely stems from the different mix of patients in different ICU settings, varying exposure to risk factors, and varying frequency of platelet count determination. The use of 100 x 10^3/mm^3 versus 150 x 10^3/mm^3 for the definition of thrombocytopenia is somewhat arbitrary. The risk of spontaneous bleeding is not significantly increased until the platelet count decreases below 20 x 10^3/mm^3, although clinicians often intervene much earlier.[12, 24, 25] A relative decline in platelets is not typically considered in studies evaluating the occurrence of general thrombocytopenia. Although a relative decrease in platelets may be a sign of a specific immune-mediated thrombocytopenia (e.g., HIT), the risk of bleeding is associated with the absolute count. Previous investigators generally have based their definition of thrombocytopenia on one platelet count below a specific threshold; however, we required two consecutive platelet counts below 150 x 10^3/mm^3. This definition limited the possibility of overestimating the frequency of thrombocytopenia based on one spurious platelet count result. As identified in our results, the variability of reported platelet counts is considerable.

This is the first study, to our knowledge, to evaluate risk markers for thrombocytopenia on admission to an ICU or CCU. The predictive potential of the admission model suggests that information available on admission to the ICU or

CCU can help identify patients who are more likely to develop thrombocytopenia. However, the improved predictive potential of the comprehensive model indicates that consideration of potential risk markers encountered during the ICU-CCU stay is also important. Although the risk markers identified by the two models were similar, the admission model included two variables that did not appear in the comprehensive model: APACHE II score and gastrointestinal bleed. However, the comprehensive model included variables associated with greater severity of illness, including pulmonary artery catheter insertion. In addition, transfusion of packed red blood cells, identified as a risk marker in the comprehensive model, may be a more specific measure of blood loss than the diagnosis of gastrointestinal bleed.

Many of the risk markers identified in this study have logical pathophysiologic explanations, and several have been associated with thrombocytopenia in previous studies. However, although these variables describe patients at highest risk, regression analysis does not establish causality. The strongest risk marker in the comprehensive model was the administration of fresh frozen plasma, which has been demonstrated to reduce platelet count.[26, 27] Whereas the conditions for which fresh frozen plasma was administered may have contributed to the development of thrombocytopenia (e.g., coagulation disorders), fresh frozen plasma has been observed to increase platelet destruction by macrophages through the effects of alloantibodies directed against the glycoprotein IIIa platelet receptor.[26, 28–30]

Packed red blood cell transfusions also were identified as a risk marker in this study and were associated with thrombocytopenia through univariate analysis in two previous studies of critically ill patients.[1, 4] Patients receiving massive red blood cell transfusions (more than a patient's normal blood volume within 24 hrs) can experience significant dilutional thrombocytopenia[7, 31, 32]; however, none of the patients with thrombocytopenia in our study received a massive blood transfusion. Nonetheless, since the decline in platelet count is inversely related to the number of units transfused,[31, 33] even moderate transfusions could have contributed to the development of thrombocytopenia, based on the definition used in our study. Significant thrombocytopenia through splenic platelet sequestration has been reported in patients receiving fewer than five units of blood.[34] Platelet consumption due to tissue injury also may have contributed.[31, 32]

Sepsis has been identified as a risk marker for thrombocytopenia in several previous studies[1–3, 5] and has been associated with increased peripheral platelet destruction in the microvasculature,[7, 35] disseminated intravascular coagulation,[7, 36, 37] and toxic bone marrow suppression.[7, 38] Musculoskeletal diagnoses (mostly trauma) and gastrointestinal bleeding were associated with thrombocytopenia in our study, likely owing to blood loss and platelet consumption. Bleeding has been identified as a risk marker for thrombocytopenia[5] and appeared to be a significant explanatory variable in our exploratory regression analysis. Respiratory failure and acute respiratory distress syndrome were also risk markers in our study and have been reported to result in thrombocytopenia through reduced platelet survival and increased sequestration in the lungs and reticuloendothelial system.[39–41]

Pulmonary artery and central venous catheters have been associated with a local or systemic antiplatelet effect, as noted by many authors.[2, 7, 42–46] Although no mechanism has been demonstrated, presence of a foreign surface possibly leads to direct platelet destruction.[7] Pulmonary artery catheters may be a marker for greater disease severity, although these two variables were not strongly correlated in our study.

Two variables, administration of aspirin and higher admission platelet count, were associated with a decreased risk of thrombocytopenia. Patients with a high platelet count at admission would require a large absolute decline in platelets to be categorized as thrombocytopenic based on our definition. Previous investigators who based their definition on a threshold platelet level have shown a lower admission platelet count to be a strong risk marker for thrombocytopenia.[5, 7] The apparent protective effect of aspirin is more difficult to explain. Although aspirin was administered to a greater proportion of patients in the CCU than in the ICU (85% vs 15%), cardiac diagnosis did not displace aspirin from the regression model, suggesting that aspirin administration was not simply a surrogate marker for cardiovascular conditions. Platelet inhibitors such as aspirin may reduce platelet consumption through inhibition of platelet aggregation, although our literature search revealed no published evidence that aspirin reduces the risk of thrombocytopenia.

In accordance with earlier studies in this area, thrombocytopenia was associated with higher

ICU-CCU and hospital mortality, as well as longer ICU-CCU and hospital stay.[1-5] This observation was not adjusted for other determinants of mortality or length of stay; however, a recent study identified thrombocytopenia as an independent marker for ICU mortality.[6] Despite this finding, thrombocytopenia is likely a risk marker for, rather than a cause of, mortality.[6]

Previous studies investigating risk markers for thrombocytopenia in critically ill patients included fewer patients than our study, and most were retrospective reviews.[1–5] In these studies, data were collected for a narrower range of potential risk markers, and various definitions of thrombocytopenia were used. These different approaches may explain the inconsistent results, although risk markers related to sepsis[1, 5] and severity of illness[4, 5] have been identified by more than one group of authors.

To our knowledge, this is the first study published on this topic from a community hospital. Therefore, the risk markers identified in this study may not be applicable to critically ill populations in other settings. However, the patient mix appears comparable in some respects with that of previous reports on this topic. The mean APACHE II score was similar to the only previous study that reported this variable (15.4 vs 17.5).[5] A higher proportion of patients with cardiovascular diagnoses were included in our study owing to the combination of ICU-CCU, although previous studies included up to 20% of patients admitted for cardiovascular conditions.[2] As among patients in the ICU in our study, previous studies reported respiratory, infectious, and gastrointestinal diagnoses as among the most common in their study cohort.[1, 2]

There are several limitations to our study. First, the low frequency of thrombocytopenia and low prevalence of some risk markers do not allow great precision in the estimation of ORs (resulting in wide CIs), and some important risk markers might have been missed. Therefore, these results should be validated in a larger cohort. Furthermore, bleeding was not assessed prospectively as a potential independent risk marker. Also, the definition of hemorrhage included a moderate decline in hemoglobin (> 1 g/dl) that may not have resulted in substantial bleeding. The influence of bleeding on the probability of developing thrombocytopenia may have been captured in other variables assessed (e.g., gastrointestinal bleeding, packed red blood cell transfusions); however, a more comprehensive assessment of bleeding as a risk marker possibly would have resulted in an improved and/or simpler model. We explored this possibility by carrying out logistic regression analysis using hemorrhage plus gastrointestinal bleed as a single variable; however, the predictive potential of the model was not improved. Another limitation is that information for some variables was obtained, at least in part, by word of mouth (e.g., previous alcohol consumption, previous heparin exposure). Whenever possible, this information was confirmed through review of the medical record. In addition, clinical outcomes occurring after discharge from ICU-CCU often were determined by retrospective chart review, which may have compromised accuracy. Finally, low-molecular-weight heparins (LMWHs) were not administered frequently during data collection, and administration of LMWHs for venous thrombosis and acute coronary syndromes has increased dramatically in recent years.[22] However, whereas LMWHs may cause thrombocytopenia, the frequency appears to be even lower than that for unfractionated heparin.[22]

Our data can be used to improve clinical decisions regarding thrombocytopenia in the critical care setting. Some identified risk markers are not amenable to change, including age, diagnoses, and admission platelet count. However, administration of transfusions and insertion of pulmonary artery catheters could be influenced. This is particularly relevant in light of recent studies questioning the liberal use of red blood cell transfusions and effectiveness of pulmonary artery catheterization in critically ill patients.[47, 48]

Whereas these results may help identify targets for intervention in patients with thrombocytopenia, they also may be used to prevent unnecessary discontinuation of beneficial therapies,[10] particularly heparin. Patients in this cohort had only a 6% predicted probability of developing thrombocytopenia if they had the mean admission platelet count (246 x 10^3/mm^3) and were not exposed to the identified risk markers. The predicted risk of thrombocytopenia increased to 56% if the patient was administered fresh frozen plasma (Figure 1). As pointed out in Results, the presence of several risk markers increased the predicted risk even more dramatically. A patient admitted with a platelet count of 200 x 10^3/mm^3 who developed sepsis and had a pulmonary artery catheter placed had a 94% predicted probability of developing thrombocytopenia. Although awareness of risk

factors may not lead to a specific intervention for such a patient, other therapies could be continued with the understanding that they are unlikely to adversely affect platelet count. Ideally, this model should be validated by using data from other critical care settings before these results are applied broadly for clinical use.

No specific drug or drug class was identified as a positive risk marker for thrombocytopenia. This finding is consistent with most studies in this area, although one study did report administration of inotropic agents and length of histamine H_2-receptor antagonist treatment as independent markers.[2] Intravenous heparin frequently results in a reduction in platelet count when administered to healthy volunteers.[49–52] As such, heparin often is implicated when thrombocytopenia develops in critically ill patients. Whereas previous studies have not identified heparin as an independent risk marker for thrombocytopenia,[1–5] these reports did not specify whether all heparin exposure was accounted for, or if they relied on retrospective chart review to calculate heparin administration. In our study, all heparin exposure carefully was documented prospectively, and heparin administration was analyzed by using several approaches. The results confirm that heparin's mild proaggregatory effect on platelets is unimportant when other risk markers for thrombocytopenia are present.

Heparin-induced thrombocytopenia, an immune-mediated syndrome that carries substantial risk of life-threatening thrombosis, must be considered when patients receiving heparin develop thrombocytopenia. Although the frequency of HIT has been estimated at 1–3%,[22] this estimate varies considerably among different populations and has not been established for patients in the ICU or CCU. The diagnosis of HIT in the critical care setting is further complicated by the high frequency of thrombocytopenia not induced by heparin, and the wide range of potential contributing factors. Unfortunately, guidelines on diagnosis of HIT do not identify factors, other than heparin, that should be considered.[22, 53] Guidelines suggest that in patients who have clinical signs of HIT, particularly those with thrombocytopenia and new thrombosis, heparin should be discontinued and alternate anticoagulation therapy begun.[53] Assays to aid in the diagnosis of HIT are recommended, but their expense and limited availability make routine use difficult. A detailed review of HIT diagnosis can be found elsewhere.[22, 53] Deciding whether to stop heparin in critically ill patients is difficult given that most patients with thrombocytopenia who are receiving heparin do not have HIT. Whereas HIT can be life-threatening, unnecessary discontinuation of heparin can increase the risk of thrombosis. Of course, in patients with active major bleeding, heparin should be discontinued or the dosage lowered. In our study, heparin was discontinued in 10 (18%) patients with thrombocytopenia, only four of whom had bleeding before or on the day of developing thrombocytopenia. There were no cases of HIT with thrombosis. Others have reported frequent discontinuation of heparin in patients with thrombocytopenia.[2, 4, 9] The risk markers for thrombocytopenia not induced by heparin identified here and further data on the occurrence of HIT in the critical care setting could be used to identify patients for whom discontinuation of heparin plus performance of laboratory tests to confirm the diagnosis of HIT should be performed.

Conclusions

Critically ill patients with specific diagnoses (sepsis, musculoskeletal, gastrointestinal, and respiratory) and those who receive transfusions (fresh frozen plasma or packed red blood cells) or pulmonary artery catheters are more likely to develop thrombocytopenia. Exposure to unfractionated heparin is not a risk marker, although discontinuation of heparin should be considered if patients are bleeding and when clinical signs of HIT are present. These results narrow the extensive list of factors previously reported to be associated with thrombocytopenia and help define when intervention may or may not be appropriate. Additional research on the validity of this model in other critically ill populations, and on the frequency of HIT in critically ill patients, would further clarify treatment decisions in patients with thrombocytopenia.

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